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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,539	10/22/1999	NICHOLAS M. DEAN	ISIS-3013	7420
32650	7590	01/06/2004	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103			ZARA, JANE J	
			ART UNIT	PAPER NUMBER

1635

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/403,539

Applicant(s)

DEAN ET AL.

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37-51 is/are pending in the application.
- 4a) Of the above claim(s) 43-51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9-03. 6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communications filed 10-1-03.

Claims 37-51 are pending in the instant application.

Election/Restrictions

Newly submitted claims 43-51 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The new claims are drawn to methods of oligonucleotide administration to an organism comprising the administration of multiple penetration enhancers.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 43-51 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-1-03 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 40, lines 4-5, it is unclear what is meant by 11.5% bioavailability achieved relative to intravenous administration (e.g. Does this mean 11.5% more bioavailability relative to intravenous administration, 11.5% bioavailability of the total amount achieved via intravenous administration, or 11.5% less bioavailability achieved relative intravenous administration? It appears from figure 4 in the specification that the alternating MMI/phosphorothioate oligonucleotide 14283 gives less overall bioavailability compared to 14182 MMI oligonucleotide, and that the column representing % bioavailability is misleading in that it is merely the ratio of IV systemic/Oral systemic availability, not an actual comparison of bioavailability between the two oligonucleotides). Appropriate clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 37, 38, 40 and 41 are rejected under 35 U.S.C. 102 (e) as being anticipated by Muller et al.

Muller et al (USPN 5,744,460) teach the oral (alimentary) administration of oligonucleotides comprising phosphorothioate or methylene (methylimino) (MMI) modified internucleotide linkages for increasing oligonucleotide stability and target binding, as well as oligonucleotides comprising at least one MMI and one phosphodiester internucleotide linkage, which oligonucleotides have increased stability and are preferably administered to an organism via their alimentary canal (See col. 7, line 52-col. 8, line 57; col. 43, line 50-col. 45, line 51).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al in view of Agrawal et al.

The claims are drawn to a method of administering an oligonucleotide to the alimentary canal of an organism comprising an oligonucleotide having at least one internucleoside linkage that is a methylene methylimino (MMI) backbone modification, and at least one phosphodiester linkage, or optionally comprising alternating MMI and phosphodiester internucleoside linkages.

Muller et al (USPN 5,744,460) teach oligonucleotides comprising modified internucleotide linkages including phosphorothioate or MMI linkages for increasing oligonucleotide stability and target binding, as well as teaching oligonucleotides comprising at least one MMI and one phosphodiester internucleotide linkage, which oligonucleotides have increased stability and are preferably administered to an organism via their alimentary canal (See col. 7, line 52-col. 8, line 57; col. 43, line 50-col. 45, line 51).

Muller et al do not teach the alimentary administration of oligonucleotides with alternating MMI and phosphodiester internucleotide linkages.

Agrawal et al (USPN 5,591,721) teach the oral administration of oligonucleotides comprising variously modified internucleotide linkages for increasing oligonucleotide stability (see col. 3, line 49- col. 4, line 5; cols. 13-14; claims 1 and 2).

It would have been obvious to one of ordinary skill in the art to incorporate modified internucleotide (non-phosphodiester) linkages into oligonucleotides because Muller et al and Agrawal et al both teach the incorporation of at least one non-phosphodiester internucleotide linkage into oligonucleotides for increasing oligonucleotide stability. One of ordinary skill in the art would have expected that incorporation of non-phosphodiester internucleotide linkages including phosphorothioate and MMI modified linkages would increase the stability of the oligonucleotides following oral or alimentary administration because Muller et al taught the incorporation of such non-phosphodiester linkages, including MMI linkages, preferably for oral administration of oligonucleotides and Agrawal et al taught the increased in vivo stability of oligonucleotides comprising at least one non-phosphodiester internucleotide linkage. One of ordinary skill in the art would have been motivated to incorporate various configurations of modified internucleotide linkages relative to phosphodiester linkages into alimentary delivered oligonucleotides because the configuration of modified (e.g. MMI or phosphorothioate linkages) and non-modified internucleotide linkages was a matter of design choice at the time the invention was made (e.g. see Muller at col. 8, lines 19-53 and Agrawal at col. 3, lines 50-64), and, according to the instant

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specification, no increased in vivo stability has been provided by the particular configuration comprising alternating MMI/phosphodiester internucleotide linkages compared to other configurations of modified/non-modified linkages.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.


Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the

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status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.


RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

December 19, 2003